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(54) Title: MATRIX METALLOPROTEINASE INHIBITORS AND THEIR THERAPEUTIC USE

(57) Abstract

A matrix metalloproteinase inhibitor is used for the treatment of a subject of a subject susceptible to or exhibiting a condition that can be treated with the inhibitor, wherein the treatment is conducted after surgical operation on the subject, and wherein the inhibitor exhibits an IC_{50} of below 100 μM with respect to matrix metalloproteinase and causes no or a partial reduction in levels of tumour necrosis factor.

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MATRIX METALLOPROTEINASE INHIBITORS AND THEIR THERAPEUTIC USE

Field of the Invention

This invention relates to the therapeutic use of compounds that inhibit matrix metalloproteinases.

Background of the Invention

Compounds having the ability to inhibit matrix metalloproteinases (MMP) and optionally also the release of tumour necrosis factor, e.g. TNFα, are described in US Patent Applications Serial Nos. 08/539,578, filed May 10, 1995, and 08/644,381, 08/644,383, 08/644,797 and 08/644,802, all filed May 10, 1996, and in WO-A-9513289, PCT/GB96/01135, PCT/GB96/01136, PCT/GB96/01137, PCT/GB96/01138, PCT/GB96/02438 (and corresponding US Application filed Oct. 5, 1996) and PCT/GB96/02439. Various effects of these inhibitory activities are described, as are suitable formulations and dosages. The specifications of all these Applications are incorporated herein by reference.

Other compounds of this general type are also known. Activity can be determined by any or all of the tests described in Examples A-G of WO-A-9611209 (described herein as "Example A" etc).

Summary of the Invention

This invention is based on the appreciation that compounds having particularly valuable properties are of the type which reduces circulating levels of TNFα with or without activity against the classical MMP's, and that circulating levels of interleukin-1β (and also IL-6) may also be reduced. This effect may be defined in terms of a specific range of activity in defined models for both TNF and IL-1β effects. The benefits arising from this invention are due to two factors. Firstly, there is synergy between TNFα and IL-1β in the body, so that a partial reduction in both of these may well have a larger effect clinically than a total reduction in just one of them (that is TNFα). Secondly, a complete reduction in

TNFα levels may b detrimental. According to this invention, the combined partial inhibition of these two cytokines should overcome this detrimental influence and yet provide as good if not better efficacy.

In particular, compounds to which this invention relates have two or more of characteristics x, y and z, wherein:

x = MMP Inhibition, in terms of IC_{50} according to Example a, b or c (see above).

y = TNFα Inhibition, in terms of IC_{50} according to Example D of Application No. PCT/GB96/01136.

z = IL-1 Inhibition, in terms of Example D of Application No. PCT/GB96/01136, modified by using a commercially-available IL-1β kit (R & D Systems) to assay the supernatant for IL-1β, determining the activity in the presence of 1 mM inhibitor or dilutions thereof by comparison to activity in a control devoid of inhibitor, and reporting IC_{50} as that inhibitor concentration effecting 50% inhibition of the production of IL-1β.

x is below 10^{-4} M, preferably below 10^{-6} M, more preferably 10^{-6} M to 10^{-9} M.

y is below 10^{-4} M, preferably 10^{-4} M to 10^{-7} M, more preferably 5×10^{-5} M to 10^{-6} M.

z is below 10^{-4} M, preferably 10^{-4} M to 10^{-7} M, more preferably 5×10^{-5} M to 10^{-6} M.

The range for z is especially interesting, since it is distinct from most prior art compounds having characteristic x. Nevertheless, this invention relates to compounds having all three characteristics, or any two characteristics with relative inactivity according to the other, eg. IC_{50} above 5×10^{-4} M.

Compounds as defined above may be used in a method of treatment (which term includes prevention and prophylaxis) of the animal, and especially human, body, in post-operative care (whether in or out of hospital). The treatment regime may be a continuation of that given before the operation, e.g. for arthritis, asthma, cancer or any

other condition susceptible to treatment with a MMP inhibitor. They may also be used where the subject is susceptible to the recurrence of lymphoma.

Description of the Invention

Compounds that meet the criteria given above are described in the specifications identified above. Specific examples of such compounds are given in the Table, below. The first and second listed compounds, and the third on the second page are in WO-A-9513289; the last two are in PCT/GB96/01136; and the others are in WO-A-9611209; reference should be made to the formulae therein. Suitable compositions, dosages etc. of such compounds are also described in the specifications identified above. The same considerations may be applied in use of the present invention.

Evidence is emerging from clinical studies conducted using specific molecular antibodies against TNFα that a complete reduction of TNFα levels in the blood of patients with rheumatoid arthritis gives rise to relatively high frequency of decidedly negative side-effects. These are of two forms, one being a reduction of the body's resistance to infection from outside agents. The frequency of serious infections in these patients is significantly increased. Secondly, an increase in the incidence of cancer in these patients, i.e. lymphoma, may occur. These symptoms may be due to the same effect, namely a reduction in the body's resistance to "foreign" agents.

Compounds of the type generally described herein may thus be particularly useful for the therapeutic indications described in the specifications of the Applications identified above. Thus, for example, the compounds of WO-A-9513289 may be useful for the expanded range of indications described in WO-A-9611209.

Reduction of the potential side-effects of cancer or infection may be particularly beneficial following surgery. In particular, post-operative infection in patients undergoing operation for cancer removal or, for example,

hip or other joint replacement, may be treated. Treatment is enhanced in situations where the potential enhancement in susceptibility to infection due to TNF reduction is coincident with the treatment of the disease. In other words, a suitable MMP inhibitor may be used to treat cancer patients concomitant with surgery, where that treatment may give rise to an increased tendency to post-operative infection, such as a nosocomial infection. Similarly, such a compound may be used during and after hip replacement and for the treatment of rheumatoid arthritis or osteoarthritis. The partial inhibition of TNF and optionally also of IL-1 rather than total TNF inhibition coincident with MMP inhibition is intended to give a benefit in reducing potential side-effects that the surgery had made the patient prone to. Further, the compounds defined herein are of benefit in reducing the occurrence of lymphoma.

					IC_{50} (μM)	
R	R^1	R^2	R^3	R^4	TNF	IL-1
Ac	H	H	i-Bu	CH_2Ph	10.2	17.5
H	H	H	i-Bu	CH_2Ph	22.7	22.6
Ac	H	H	CH_2SMe	CH_2Ph	31	38
H	H	H	CH_2SMe	CH_2Ph	9	62
Ac	$(CH_2)NPhMn$	H	i-Pr	CH_2Ph	14	51
Ac	$(CH_2)_4CO_2Me$	H	n-heptyl	CH_2Ph	11	12.9
Ac	$(CH_2)_3NPhMn$	H	CH_2SMe	CH_2Ph	5.5	11.2
Ac	$(CH_2)_3NPhMn$	H	n-Pr	CH_2Ph	9.3	8.6
Ac	$(CH_2)_3NPhMn$	H	CH_2SMe	CH_2-3-indolyl	15.8	1A
H	$(CH_2)_3NPhMn$	H	CH_2SMe	CH_2-3-indolyl	7.1	47
Ac	$(CH_2)_3NPhMn$	H	i-Bu	CH_2-3-indolyl	16.8	1A
H	$(CH_2)_3NPhMn$	H	i-Bu	CH_2-3-indolyl	35	1A
Ac	$(CH_2)_4CO_2Me$	H	i-Bu	CH_2-3-indolyl	38	22
Ac	$(CH_2)_3NPhMn$	H	i-Pr	$(CH_2)_3NHBoc$	15	37
Ac	$(CH_2)_3NPhMn$	H	i-Bu	t-Bu	11.6	22
Ac	$(CH_2)_3NPhMn$	H	i-Bu	$C(Me)_2SMe$	6.4	24
Ac	$(CH_2)_3NPhMn$	H	i-Bu	CH_2Ph	5.8	11.2
H	$(CH_2)_3NPhMn$	H	i-Bu	CH_2Ph	6.2	18.7
Ac	(S)-$(CH_2)_3NPhMn$	H	i-Bu	CH_2Ph	6.6	21.8
H	(S)-$(CH_2)_3NPhMn$	H	i-Bu	CH_2Ph	24	1A
Ac	$(CH_2)_2Ph$	H	i-Bu	CH_2Ph	24	1A
Ac	$(CH_2)_4CO_2Me$	H	i-Bu	CH_2Ph	29	11
Ac	$(CH_2)_3SAc$	H	i-Bu	CH_2Ph	5	25
H	H	$(CH_2)_3NPhMn$	i-Bu	CH_2Ph	8	6
H	H	$(CH_2)_2NPhMn$	i-Bu	CH_2Ph	25	4

CLAIMS

1. Use of a matrix metalloproteinase inhibitor for the manufacture of a medicament for the treatment of a subject susceptible to or exhibiting a condition that can be treated with the inhibitor, wherein the treatment is conducted after surgical operation on the subject, and wherein the inhibitor exhibits an IC_{50} of below 100 μM with respect to matrix metalloproteinase and causes no or a partial reduction in levels of tumour necrosis factor.

2. Use of a matrix metalloproteinase inhibitor for the manufacture of a medicament for the treatment of a subject susceptible to or exhibiting a condition that can be treated with the inhibitor, and susceptible to recurrence of lymphoma, and wherein the inhibitor exhibits an IC_{50} of below 100 μM with respect to matrix metalloproteinase and causes no or a partial reduction in levels of tumour necrosis factor.

3. Use according to claim 1 or claim 2, wherein the IC_{50} (MMP) is below 1 μM.

4. Use according to claim 3, wherein the IC_{50} (MMP) is between 1 nm and 1 μM.

5. Use according to any preceding claim, wherein the IC_{50} (IL-1) is between 0.1 and 100 μM.

6. Use according to claim 5, wherein the IC_{50} (TNFα) is between 1 and 50 μM.

7. Use according to any preceding claim, wherein the IC_{50} (TNFα) is below 100 μM.

8. Use according to claim 7, wherein the IC_{50} (TNFα) is between 0.1 and 100 μM.

9. Use according to claim 7, wherein the IC_{50} (TNFα) is between 1 and 50 μM.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02746

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 13289 A (CHIROSCIENCE LIMITED) 18 May 1995 cited in the application see the whole document	1-9
P,X	WO 96 11209 A (CHIROSCIENCE LIMITED) 18 April 1996 cited in the application see the whole document	1-9
E	WO 96 35711 A (CHIROSCIENCE LIMITED) 14 November 1996 cited in the application see the whole document	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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